Passive Smoking and Lung Cancer among Japanese Women

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Suminori Akiba, Hiroo Kato, and William J. Blot1

Radiation Effects Research Foundation, Hiroshima, Japan [S. A., H. K.], and National Cancer Institute, Bethesda, Maryland 20892 [W. J. B.].

ABSTRACT

A case-control study conducted in Hiroshima and Nagasaki, Japan, revealed a 50% increased risk of lung cancer among nonsmoking women whose husbands smoked. The risks tended to increase with amount smoked by the husband, being highest among women who worked outside the home and whose husbands were heavy smokers, and to decrease with cessation of exposure. The findings provide incentive for further evaluation of the relationship between passive smoking and cancer among nonsmokers.

INTRODUCTION

As part of a case-control investigation of lung cancer among atomic bomb survivors conducted primarily to evaluate the interactive roles of cigarette smoking and ionizing radiation (1), data were collected on the smoking habits of the subject's spouses and parents. Herein we report the effect of exposure to such passive smoking, focusing on married women who had never smoked themselves.

MATERIALS AND METHODS

Since 1951 a cohort of 110,000 Hiroshima and Nagasaki atomic bomb survivors has been followed by the RERF.² formerly called the Atomic Bomb Casualty Commission (2). During the period 1971 to 1980, 525 newly diagnosed cases of primary lung cancer (Eighth Revision ICD 162.1) were identified among cohort members. The cases were ascertained from the Hiroshima and Nagasaki Tumor and Tissue Registries, the RERF mortality, surgical, and autopsy files, and Hiroshima University medical records. The diagnosis was based on biopsy or surgical pathology findings for 25%, on autopsy findings for 28%, on cytology for 4%, and on radiological/clinical findings for the remaining 43%. Since the cohort represents a fixed population that is aging over time and is older than the general population, the ages at diagnosis were higher than usual for lung cancer in Japan: the means were 72.1 for males and 70.2 for females; the ranges were 36 to 94 for males and 35 to 95 for females.

Controls were selected from among cohort members without lung cancer, 2 for each case in Hiroshima and 3 for each case in Nagasaki. The controls were individually matched to the cases with respect to yr of birth $(\pm 2 \text{ yr})$, city of residence (Hiroshima or Nagasaki), sex, and whether or not they were among the 20% of the cohort purticipating in the program of biennial medical examinations given at RERF. In addition, controls were matched to cases on vital status. Since most of the cases had died, most of the controls were also deceased. The deceased controls were chosen according to the above-mentioned matching criteria, plus year of death $(\pm 3 \text{ yr})$, and they were selected from among all causes of death except cancer and chronic respiratory disease. The distribution of the controls series is as follows: alive, 13%; deceased from cerebrovascular disease, 26%; from coronary heart disease, 13%; from other circulatory disease, 12%; from acute respiratory

disease, 9%; from digestive disease, 8%; from accidents, 6%; and from other causes, 14%.

Interviews were sought during 1982 with all cases and controls, or their next of kin, who lived in Hiroshima and Nagasaki. The interviewers were aware that the study concerned lung cancer, but they were not told of the case-control status of the study subjects. A structured questionnaire was used to obtain histories of cigarette smoking and demographic, medical, occupationall and other factors. If the individuali was married, inquiry was made about the smoking status of the spouse, including the average number of cigarettes smoked per day, age started smoking, and, for those who stopped, the age of cessation of smoking. Using this information, together with the numbers of yr the husband and wife lived together, an index of exposure to the spouse's smoking was calculated. In addition, a single question was asked regarding whether the subject's mother and/or father smoked when the subject was living at home as a child.

OR were calculated as measures of the association between lung cancer and passive smoking and other factors (3). Estimates of the OR, and corresponding significance tests, were obtained by a conditional logistic regression analysis for matched data (4). Tests for trend used consecutive integers for levels of the ordered categories. Because there were a priori hypotheses that passive smoking might increase lung cancer risk, all significance tests for passive smoking effects were one-sided, with 90% CI used for interval estimates of the OR. Because interest focused on spouse smoking patterns, eliminated from the analyses were the one case and 6 controls among males and the 4 cases and 7 controls among females who were never married. Among the married individuals, almost all had been married to only one spouse. Among those with more than one spouse, information was available only for the most recent. Also excluded from each table were individuals with missing data for the variable being studied.

RESULTS

Interviews were obtained for 428 cases and 957 controls, respectively, 81% and 82% of the eligible cases and controls. The two primary reasons for nonresponse were the refusal of next of kin to answer questions about their deceased relatives and the decision not to attempt to locate next of kin for subjects who had moved out of Hiroshima or Nagasaki. The distribution of informants is given in Table 1, indicating that the information for most of the subjects was provided by next of kin. The type of respondent, however, was similar for cases and controls.

Table 2 shows the lung cancer OR according to the smoking status (smoker versus never smoked) of the subjects and their shouses. In both sexes there was an increased lung cancer risk associated with direct smoking. As indicated, almost all (93%) of the male lung cancer cases were smokers, but only a minority (38%) of the women with lung cancer in this population were reported to have ever smoked. Although not shown, the OR increased with the numbers of cigarettes usually smoked per day during adulthood for both men and women. Among males who smoked 1 to 9, 10 to 19, 20 to 29, and 30+ cigarettes per day, the OR were 1.7, 1.8, 3.4, and 9.7, respectively (P for trend < 0.01). Among females who smoked 1 to 9, 10 to 19, and 20+ cigarettes per day, the OR were 1.9, 2.0, and 4.9 (P for trend < 0.01). Table 2 shows that among female nonsmokers married to smokers, there was an elevated risk for lung cancer (OR 1.5; 90% CI = 1.0 to 2.5; P = 0.07). Although similar increases associated with smoking habits of spouses were observed for female smokers and for male nonsmokers and smokers, suffi-

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¹To whom requests for reprints and correspondence from outside the United States should be addressed, at Department of Epidemiology and Statistics, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Hiroshima 730, Japan (S. A.), and from the United States, at Epidemiology and Biostatistics Program, National Cancer Institute, Landow Building 3C16, Betheada, MD 20892 (W. J. B.).

²The abbreviations used are: RERF, Radiation Effects Research Foundation; OR, odds ratio(s); Cl. confidence interval(s).

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Table 1 Percentage distribution of respondents

	Sex of study subject (%)					
	1	Male	Female			
Respondent	Case	Control	Case	Control		
Self	6	7	16	19.		
Spouse	51	48:	12	111		
Child	23	22	33	33		
Daughter-in-law	11	12	18	17.		
Others	10	10	21	19.		
Total %	100:	100	100	1:00		
	264	595	164	362		

Table 2 Odds ratios for lung cancer according to smoking status of the subjecand his/her spouse

Sex of subject	Subject: smoker	Spouse amoker	Case	Control	OR*	90% C1°
Maic	No	No	16	101	1105	
		Yes	3	9	1.8	(0.5, 5.6)
	Yes	No	190	388	3.4	(2.1, 5.5)
		Yes	51:	86	4.2	(2.4, 7.3)
Female	No	No	21	82	1'.0"	
		Yes	73	188	1.5	(110, 2.5)
	Yes	No	8	14.	2.2	(0.9, 5.1)
		Yes	50	56	3.6	(2.1, 6.1)

Odds ratio and 90% CI from matched analysis:

Referent category

Table 3 Odds ratios for lung cancer among nonsmoking women according to husband's usual daily consumption of cigarettes

No. of cigarettes ausband usually smoked/day	Case:	Control	OR*	90% CI*
0	21	82	1.0	
1-19	29	90	1.3	(0.7, 2.3)
20-29	22	54	15	(0.8, 2.8)
30+	12	23	2.1	(0.7, 2.5)

Odds ratio and 90% CI from matched analysis.

Table 4 Odds ratios for lung cancer among nonsmoking women according to husband's duration of smoking eigerettes while married

Yr husband smoked cigarettes	Case	Control	OR*	90% CT*
0	21	82	1.0	
1-19	20	30:	2:1	(1.0, 4.3)
20-39	29	81	1.5	(0.8, 2.7)
40+	22	59	1.3	(0.7, 2.5)

Odds ratio and 90% CI from matched analysis.

cient data for detailed analyses of passive smoking patterns were available only for female nonsmokers.

The data for nonsmoking women are categorized in Table 3 according to the number of cigarettes the husband usually smoked per day during adulthood. There was an increasing lung cancer risk with increasing amount smoked per day by the husband, with the OR slightly exceeding 2-fold for women whose husbands were heavy smokers. No monotone trend of increasing risk associated with increasing duration of exposure to husband's smoking was found (Table 4). Risks according to time of exposure are examined in Table 5. The odds ratios were lower among "ex-passive smokers" than among women who had been exposed to their husbands' smoking within the past 10 yr. The reduction in risk with cessation of exposure remained after adjusting for the amount of cigarettes smoked per day by the spouse.

Table 5 Odds ratios for lung cancer among nonsmoking women according to recency of exposure to husbands' smoking

Time of exposure	Case	Control	OR*	90% CT*
None	21	82	1.0	
Not exposed within last 10 yr	31	87	1.3	(0.9; 2.4)
Exposed within last 10 yr	40	85	1.8	(1.0, 3.2)

Odds ratio and 90% CI from matched analysis.

Table 6 Odds ratios of lung cancer among nonsmoking women according to their occupation and their hasblands' smoking status

Occupation of subject	Husband's smoking status	Case	Control	OR*	90%-C1*
Housewife'	Néver	6	20	1.0	
	Light	111	34	0.9	(0.4, 2.1)
	Heavy	15	35	1.5	(0.7, 3.3)
White collar	Never	7.	23	1.0	(0.4; 2.4)
	Light	9.	20:	1.7	(0.7, 4.5)
	Heavy	8	16	1.6	(0.6, 4.1)
Bive collar	Never:	6	24	1.1	(0.4, 2.9)
	Light	5	22	0.5	(0.2, 1.5)
	Heavy	7	6	10.4	(1.6, 66.7)

^{*}Light, husband smoked less than 20 cigarettes/day; heavy, husband smoked 20 or more cigarettes/day.

Odds ratio and 90% CI from matched analysis.

'Housewife defined as woman who was employed outside the home for no more than 10 yr.

Reference category.

Office and sales workers

As shown in Table 6, the risk of lung cancer tended to increase in relation to exposure to the husband's tobacco-smoke for each of housewives, white collar, and blue collar workers. The highest odds ratio occurred for women who had blue collar jobs and were married to men who smoked one or more packs of cigarettes per day, but the numbers involved were small.

The odds ratios from the matched logistic regression analyses presented in Tables 2 to 6 are generally similar to unadjusted odds ratios that can be calculated from the cross-products of the numbers of exposed and unexposed cases and controls, indicating that confounding in unadjusted analyses by age, city, vital status, and yr of death (the matching factors) is not substantial. We also assessed whether the associations with passive smoking were consistent across the various strata defined by the matching factors. The numbers of subjects in several of the categories became quite small with this fine a cross-classification, but the trends with husbands' smoking tended to be seen throughout, with no strong differences by age group or by city of residence. The trends were also apparent for each type of informant (self, husband, child, and other); in particular the elevated risk for heavy relative to nonexposure to husbands' smoking was detected when data were reported by the husbands or subjects themselves. Radiation exposure was also examined as a potential confounder and effect modifier. No significant influence of radiation dose on the passive smoking association was detected, although the trends with passive smoking seemed stronger among the unexposed.

Information on the histological types of lung cancer was unavailable for 43% of the cases who were diagnosed only on radiological or clinical evidence. We conducted separate analyses among those with and without a pathological confirmation of lung cancer and found increased risks associated with passive smoking for both groups. The OR among nonsmoking women

Individual reported never to have smoked cigarettes.

These "ex-passive smokers" are those whose busbands quit smoking 10 or more yr prior to the diagnosis of lung cancer (or 10 or more yr prior to the date of selection for controls) or those who were not living with their husbands because of separations, divorce, or his death 10 or more yr prior to the diagnosis.

Excludes 5 cases and 34 controls who were farmers.

n.arried to smokers was 1.4 for the cases and their matched controls with a histologically confirmed diagnosis, and 1.6 for those with a clinical/radiological diagnosis. Among women with a histological diagnosis, adenocarcinoma was the predominant cell type, but the distribution of histological types varied by smoking status (Table 7). The percentage of squamous and small cell carcinoma was much higher among smokers than nonsmokers. Although based on small numbers, there were also more squamous and small cell cancers among nonsmoking females whose husbands smoked.

Responses to the question on parental smoking while the subject was a child were provided for only two-thirds of the subjects. Among these the mothers of the subjects were reported to be smokers for 13% of the cases and 17% of the controls, and the fathers, for 67% of the cases and 66% of the controls. Hence there was no overall increased risk associated with parental smoking, nor was there any significant increase after stratifying by smoking status of the subject. Among male smokers, the OR for lung cancer associated with maternal smoking was 1.1.

DISCUSSION

The results from this case-control study suggest that there may be a moderate excess in lung cancer risk associated with passive smoking. The odds ratios for lung cancer among non-smoking women tended to increase with amount smoked by their husbands, a trend seen among housewives as well as women who worked outside the home. The highest odds ratios among nonsmokers were for women who worked in blue collar jobs whose husbands were heavy smokers, women presumably with the highest exposure to environmental tobacco smoke. There was little association with parental smoking or with expassive smoking, suggesting that cessation of exposure may lower risk.

The findings are generally consistent with results of a national cohort study of mortality among Japanese women (5) and of several epidemiological investigations conducted elsewhere inthe world (6-8). Updated follow-up for the period 1966 to 1981 of the study conducted among an adult population selected from multiple areas throughout Japan, excluding Hiroshima and Nagasaki, showed a gradient in mortality with amount smoked by the husband (9). The increase in risk reached 90% among those whose husbands smoked 20 or more cigarettes per day, a figure in line with the 2-fold excess for 30 or more cigarettes per day of smokers in our study. The similarity in results, despite different methodological approaches, suggests that the association between lung cancer and passive smoking is not an artifact of recall bias which can affect retrospective studies. Furthermore, we were unable to identify any strong confounding factors, including radiation exposure, that may have accounted for the passive smoking association.

It is noteworthy that a recent survey in Kyoto, Japan, found significantly elevated levels of cotinine, the major metabolite of nicotine, in the early morning urine of nonsmokers who lived in households with smokers or worked in offices/factories with

Table 7: Percentage histological distribution of lung cancers among females according to their and their husbands' smoking status

		Cell type (%)			
	Husband smoker	Squamous or small cell cancer	Adenocarcinoma or large cell cancer		
No	No	0	100		
	Yes	16 /	84		
Yes		58	42		

smokers (10). The cotinine concentrations among nonsmokers living with 2-pack-a-day smokers were roughly equivalent to the cotinine levels of smokers of less than 3 cigarettes per day. Precise estimates of the lung cancer risk associated with this level of smoking are not available, since not many smoke so few cigarettes per day. However, 3 well-known prospective studies of mortality among smokers [the American Cancer-Society study involving nearly 1 million volunteers (11), the 16yr follow-up of 250,000 United States veterans (12), and the 20-yr follow-up of 34,000 British doctors (13)] found relative risks of lung cancer of 4.6, 4.8, and 7.8 among 1 to 9, 1 to 9, and I to 14 cigarette-per-day smokers, respectively. Linear interpolation between these values and the base-line level of 1.0 for nonsmokers would yield estimated relative risks for 1 to 2 cigarette-per-day smokers of nearly 2-fold, about the same order of increase observed for "heavy" passive smokers in this study. Hence, if the Kyoto results (10) are applicable elsewhere,3 and if urinary cotinine levels reflect levels of exposure to the carcinogenic substances in tobacco smoke, then the observed magnitude of the increased lung cancer risk among passive smokers in Japan seems not greatly out of line with what might be expected based on their exposure to environmental tobacco smoke.

It should be noted that the risk ratios for lung cancer associated with direct smoking (as shown in Table 2) were lower in this case-control study than typically found in case-control and cohort investigations in other countries (14). The lower OR among smokers in part arises from our selection, in order to minimize respondent bias, of controls matched to cases on vital status, which led to the inclusion of some controls who died of smoking-related diseases. However, lung cancer risk ratios generally similar to those in this study were also reported in the prospective study of Japanese adults (9). Because of the lower relative risks of lung cancer among smokers in Japan, differences in the OR between direct and passive smokers are not as high as in western countries. Indeed, we found OR for "heavy" passive smokers to be nearly equal those for women who were reported to be light smokers themselves. While such similarity was unexpected, characteristics such as the size and style of residential units might result in a higher environmental-todirect tobacco smoke exposure ratio in Japan (and thus less of a difference in OR for lung cancer between passive and direct smokers). This in fact is suggested by the comparison of the cotinine analyses between Japan and Great Britain (10, 15), where the ratio of cotinine levels in passive compared to direct smokers was considerably higher in Japan. Our finding that lung cancer risk among nonsmokers may be less closely related to duration of exposure to tobacco smoke, the major determinant of hing cancer risk among smokers (13), than to intensity and recency of exposure also may be noteworthy. Such a difference might contribute to a higher ratio in Japan of lung cancer risks in passive compared to direct smokers, since the current prevalence of smoking is higher in Japan than in either Great Britain or the United States, but the marked temporal increase in smoking began later (9, 16).

The present study did not replicate the finding of a casecontrol study in Louisiana which showed a higher risk among male smokers whose mothers had smoked (7). Although we did find higher percentages of smokers among both cases and controls and among both men and women whose parents had been smokers, there was no elevation in the OR among smoking

^{*}There is some question about their generalizability, since cotinine levels among heavy paneire smokers in Kyoto-were about one-seventh the levels in average smokers, in contrast to about one-fiftieth in a recent British study (15). In both studies, however, the urinary levels increased in proportion to estimated paneive smoking exposure.

Japanese men or women associated with maternal or paternal smoking. However, it was often difficult for the respondents to provide information on parental smoking, and data on this exposure were missing for about one-third of the subjects.

One of the concerns in this study was the adequacy of data provided by surrogate respondents. Only a minority of the patients could be interviewed directly because of the often fatal outcome of lung cancer and the need to include cases diagnosed as early as 1971 in order to assemble sufficient numbers of subjects for analysis. The distribution of respondent types was comparable between cases and controls so that response bias is unlikely, but the possibility of poor quality information for both cases and controls existed. We could evaluate this possibility, however, since many of the cases and controls had provided information on their smoking habits in routine RERF surveys conducted in the 1960s when all study subjects were alive (1, 2). The data in Table 8 indicate very high concordance in the identification of a female as a nonsmoker or smoker by a next of kin in 1982 and by the woman herself in the 1960s. In addition to providing some confidence that the data provided by surrogates are adequate, the confirmation of nonsmoking status by a next of kin argues against the possibility that Japanese women tend to report themselves as nonsmokers whenthey actually smoke. The 1982 survey revealed a higher percentage of male smokers than reported earlier, but the increase was both for self as well as next-of-kin interviews and may reflect an actual increase in smoking prevalence over time. Questions about the smoking habits of spouses were not asked in the surveys in the 1960s, so that self versus surrogate reporting on this variable cannot be assessed directly. In our study, however, there were no significant differences in the passive smoking trends according to respondent type. In particular, an increased OR was seen for nonsmoking women whose husbands were heavy smokers when the data were reported by the husbands themselves.

Another concern in this case-control study was the reliability of the diagnoses of lung cancer. Forty-three % of the cases were diagnosed solely on clinical and/or radiological evidence. The percentage was high in large part because the cohort being followed was elderly, and surgical or biopsy procedures were less likely to be performed on older patients. The OR associated with passive smoking, however, were similar when calculations were restricted to histologically confirmed cases. We also calculated OR after deleting 23 cases and their matched controls for whom a diagnosis of possible or probable lung cancer was made only on radiological grounds and who had survived 5 or more yr (all were in fact living as of January 1984), since the diagnoses for at least some appear to be questionable. Little change was noted. Smoking has been shown to induce all types

Table 8. Comparison of smoking status from the 1982 on RERF surveys in 1964 to 1968

The numbers of paired responses for the 4 sex-informant categories below are 58, 679, 45, and 92, respectively.

Sex of	Informant in 1982	1964-1968	1982 smoking status (%)		
subject		current.	Never-	Smoker	
Male	Self	No	18	14	
		Yes	0	68	
	Surrogate	No.	12	13	
		Yes	1	74.	
Female	Self	No	87.	0	
		Yes	0	13	
	Surrogate	No	65	3	
		Yes	0	32	

of lung cancer, but its effect is greater for squamous and small cell carcinoma than adenocarcinoma (17). Whether passive smoking might have the same predilection for squamous cancers is not clear, but our limited histological data (Table 7) are consistent with this notion. It is of interest that the highest OR for passive smoking has been reported from a case-control study. in Greece (6, 18, 19) where the cases were limited to lung cancers other than adenocarcinoma.

In summary, the results of this investigation suggest that exposure to environmental tobacco smoke may increase the risk of lung cancer among nonsmokers. The findings, from one of the two areas of the world where the possibility of a passive smoking hazard was first postulated, add to an accumulating body of evidence on the issue. While the total evidence is not definitive and not all studies show significantly positive associations (20-22), the results are suggestive enough to warrant further evaluation in larger studies where passive smoking exposures can be more fully quantified.

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